IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	CATCHESIDE	Examiner:	D. LAMBERTSON
Serial No.:	09/751,962	Group Art Unit:	1636
Filed:	DECEMBER 29, 2000	Docket No.:	10552.13USC1
Title:	REAGENTS AND METHODS FOR DIVERSIFICATION OF DNA		

CERTIFICATE UNDER 37 CFR 1.10:
"Express Mail" mailing label number: EV372669190US
Date of Deposit: February 26, 2004

I hereby certify that this paper or fee is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, Mail Stop AF, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Teresa Anderson
Name: Teresa Anderson

DECLARATION UNDER 37 C.F.R. § 1.132

I, Dr. David, E.A. Catcheside, state the following:

1. I am a Professor of Biological Sciences, Deputy Head School of Biological Sciences at Flinders University, in South Australia.

2. I am the inventor of the above-identified patent application entitled "Reagents and Methods for Diversification of DNA."

3. I have read and understand the Office Action from the United States Patent Office mailed on August 26, 2003.

4. The Examiner has made a "written description" rejection of claims 1-3, 8-36, and 42-69. The Examiner asserts that the patent application as filed does not adequately describe the eukaryotic hot spots used in my method for diversifying genes. I disagree. In fact, my application as filed, together with what was known at the time the application was filed, provides thorough description of my inventive method that uses eukaryotic hot spots.

5. It is generally known that there are only about sixty (60) types of eukaryotes. See, e.g., Patterson, American Naturalist 154 (supp) (S96-S124) (1999). My patent application describes, by organism, the location of at least twenty-four (24) eukaryotic hot spots. The hotspots described in my patent application include:

1) *Saccharomyces cerevisiae* at the *arg4* loci (M Lichten and ASH Goldman Ann. Rev. Genet. 29: 423-444 1995)
2) *Saccharomyces cerevisiae* at the *his4* loci (M Lichten and ASH Goldman Ann. Rev. Genet. 29: 423-444 1995)
3) *N. crassa* at *cog*
4) *N. crassa* at *am* loci
5) *N. crassa* at *his-3* loci
6) At the mating type loci in the Basidiomycete *Schizophilum commune* (G Simchen and J Stamberg Heredity 24: 369-381 1969)
7) 5' of *cys3* in *S. cerevisiae*,
8) 5' of *his2* in *S. cerevisiae*,
9) *Schizosaccharomyces pombe* within the *ade6* gene
10) *Schizosaccharomyces pombe* 5' of the *ade6* gene
11) at *his-1* in *Neurospora crassa*
12) at *nit-2* in *Neurospora crassa*
13) near *pyr-3* in *Neurospora crassa*
14) near *sn* in *Neurospora crassa*
15) near *his-2* in *Neurospora crassa*
16) hotspots in the fungi *Aspergillus nidulans*
17) hotspots known to exist in the fungi *Schizophillum commune*
18) HOT1 in the genome of *Saccharomyces cereviseae.*
19) hotspots in maize
20) hotspots in mouse (*Mus musculus*) - close to the major histocompatibility locus
21) hotspots in humans (*Homo sapiens*) - near the gamma globulin loci
22) hotspots in Chimpanzee - near the gamma globulin loci
23) hotspots in humans near the retinoic acid alpha receptor gene
24) hotspots in humans in the region of the repeat sequences associated with Charcot-Marie-Tooth neuropathy;

My patent application describes these eukaryotic hot spots in the specification at least at page 6, line 22 - page 7, line 11 and page 20, line 10-17.

6. My patent application also describes other eukaryotic hot spots by citation to the scientific literature known at the time the above-identified patent application was filed. The well-known and described eukaryotic hot spots disclosed in the scientific literature include representatives from Fungi, Mammals and Plants. The references describing such hot spots include:

1) For the Yeast organism, the ade6 gene was found to be a eukaryotic hot spot. Specifically, the reference discloses that the ade6-M26 mutation yields up to 15 times more prototropic recombinance in the intragenic crosses. (Genetics 119: 491 (1988))

2) The results of the study by Grimm, Christian, Jürg, Bähler and Jürg Kohli identify M26 of the ade6 gene as a recombinational hot spot. (EMBO 13:5121-29 (1994))

3) The study by Virgin, Jeffery B., Genns, Metzger and Gerald R. Smith, determined the active and inactive of the trans placement of the M26 recombination hot spot. This reference identified that the M26 mutation provided an ideal control for identifying hot spot activity. (Genetics 141:39 (1995))

4) The ura-4 gene of yeast was found to be a recombinational hot spot. The article disclosing this information first recognized that homologous recombinational events are not randomly distributed through the genome. Rather, there are regions that have higher frequency of aberrant segregations and cross overs these are called hot spots. (Genetics 140: 470 (1995))

5) To ascertain whether the ade6 fragment was required for M26 hot spot activity as found in the previous literature, researchers investigated the possible effect of M26 in that region. This research discovered the ura-4 hot spot. (Genetics 140: 470 (1995))

6) The ampR gene of the organism *S. cerevisiae* was found to be a recombinational hot spot. (Genetics 127:29-51 (1991))

7) The HIS4 gene of the *S. cerevisiae* organism was discovered to be a recombinational hot spot. This reference also discloses that BIK1 as a recombinational hot spot. (PNAS 90:6622 (1993))

8) BIK1 of the yeast organism *S. cerevisiae* was also discovered by others to be a recombinational hot spot (Genetics 134: 5-19 (1993))

9) The HIS2 gene of the yeast organism *S. cerevisiae* was identified as a recombinational hot spot. (Genetics 144: 71-86 (1996))

10) The eukaryotic recombinational hot spot wx of *Z mays* (maize) was identified. (Genetics 147:815-21 (1997))

11) Similarly, two other hot spots have been identified for *Z. mays*. These two hot spots have been identified as the genes bz1 & bz2. (Plant Cell 9:1633-46 (1997)(

12) Researches have also identified recombinational hot spots in the fruit fly *D. melanogaster*. The Tp1 gene is identified as a recombinational hot spot in (Genetics 122:397-401 (1999))

13) Researchers have also identified a number of recombinational hot spots in various mammals. A general discussion of that research appears in Cell 57:937-46 (1989).

14) Researchers have identified the genes beta 2&3 of *M. musculus* (mouse) as recombinational hot spots. (Immunogenetics 31: 79-88 (1990) and EMBO 10: 681-6 (1997))

15) The Eb gene of *M. musculus* is also identified as a recombinational hot spot. Mammalian Gemone 2:123-9 (1992).

16) The Lmp-2 gene of *M. musculus* was identified as a recombinational hot spot. (Advances in Biophysics 31: 119-32 (1995) and Mammalian Genome 7: 490-6 (1996))

17) Three genes have been identified as recombinational hot spots in *H. sapiens* (human). The first was identified in International Immunology 7: 1191-204 (1995) as the gene bcl-2. The second was identified in J Human Genetics 56: 1350-8 (1995) as the gene TAP2. The same gene was also identified in Nature Genetics 12: 288-97 (1996). The third recombinational hot spot identified for *H. sapiens* (human) was reported in Immunogenetics 46: 499-508 (1997) as the gene MHC1B.

7. My patent application provides a detailed description of the location of at least twenty-four (24) eukaryotic hot spots. The scientific literature at the time my application was filed described numerous additional details about these and other hotspots. I was not the first to discover the existence of hotspots. My invention is a new method employing hot spots. My method diversifies genes. My patent application as filed, together with what was known at that time, provides thorough description of eukaryotic hot spots. Therefore, my patent application provides a complete description of my inventive method employing hot spots.

8. My patent application includes a complete and thorough description of my inventive method for diversifying genes using eukaryotic hotspots. I believe that other researchers in this field, upon reading and understanding the disclosure of my patent application, would immediately and inevitably realize the nature and characteristics of eukaryotic hotspots useful in my inventive method. Based on the disclosure of my patent application, these other researchers would readily be able to employ any eukaryotic hotspot in my inventive method. Further, using known methods such researchers could easily find additional hot spots in any of a variety of organisms. After having read and understood my patent application, these researchers could then use these newly discovered hot spots in my inventive method for diversifying genes.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

_____ By: _____

Date Dr. David E.A. Catcheside

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25 February 2004 By: DA Catheside

Date Dr. David E.A. Catheside